

Introduction to Toxicity Evaluation Session

by Frederick Sperling*

There have been invented innumerable chemical substances which enter living organisms, including humans. These may damage the liver, preserve the teeth, damage the fetus, induce cancers, cure trivial and serious diseases, destroy vermin, prolong life, increase the quality and quantity of the food supply, preserve the facade of youth for the aging and make instantaneous photographs in vibrant living color.

When a chemical enters a living organism, the blood stream carries it along until it comes to rest in or on one or more of the various organ systems. An interaction between the chemical and a reactive component of the organ then occurs. The organ reacts and the chemical is changed; biotransformed. If the organ reaction is defined as injurious by any of several criteria, the chemical is characterized as toxic. This pharmacological toxicity differs from mechanical injury, such as burns and wounds, in several important respects. One of these is that there is usually a mathematical relation between the dose and the frequency of response of individuals within a group to that dose. Such relationships are lacking after mechanical injury.

During the past few decades there has been an exponential increase in sophistication of instrumentation making possible large scientific advances. It is now possible to isolate and identify a specific chemical from all other ingredients in a soup and then to reliably measure its quantity in pico units. It is now possible to design and produce living systems with predetermined biochemical and structural characteristics from bacteria to hairless mice. It is now possible to develop mathematical and statistical models to analyze the most complex life processes ranging from the Michaelis-Menten equation to matrices. Unfortunately, along with these advances, there has not been an equally impressive increase in sophistication in toxicological theory and practice.

There have been advances in methodology ranging from the use of specially designed animal strains on the one hand to meticulous attention to animal care on the other; from using "two freshly caught temporary frogs" in an early toxicity test with acetylsalicylic acid, to using rigorous controls in animal experiments.

Yet despite instrumental, theoretical, and procedural advances, toxicological analysis remains a one-dimensional exercise analyzing multidimensional effects. There is still an over-emphasis on counting dead bodies as an index of toxicity. This is apparent in the international effort currently underway, based on collaborative studies, to standardize acute mortality tests; the LD₅₀.

Nearly all studies which involve the dose-response confine themselves to measuring frequency in a group, of mortality or of some defined morbidity parameter, as an index of effect. Small effort has been made to assemble the array of pertinent parameters into a unified index which would be indicative of actual toxicity. Such an array would encompass intensity of effect, time to onset, duration to death, if it occurs, and degree of recovery in survivors as well as time required to reach that happy state. It would include measured physiological and pathological changes. The assembling and assessment of such an array would help remove much of the guesswork about toxicity potential of long term exposure to low levels of chemicals.

It should be a task with high priority for a collaborative effort between statisticians and toxicologists to develop more realistic and useful indices of toxicity; especially for the problems of risk assessment. Indices of toxicity should not derive from subjective biases as trumpeted by the optimistic assessments of the polyannas, or the dire predictions of the Cassandras or the distortions by the media.

The papers presented at this session place a proper perspective on the problems of toxicology.

*Department of Pharmacology, Howard University College of Medicine, Washington, D.C. 20059.